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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,841	07/27/2005	Robert Wieder	601-1-134PCTUS	1291

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EXAMINER	
NATARAJAN, MEERA	
ART UNIT	**PAPER NUMBER**
1609	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,841	WIEDER, ROBERT	
	Examiner	Art Unit	
	Meera Natarajan Ph.D.	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7-13,47 and 49-59* is/are pending in the application.

4a) Of the above claim(s) *7, 8, 10, 11, 47, 50-52, and 55-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,9,12,13,49,53 and 54* is/are rejected.

7)☐ Claim(s) ~~58~~ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/14/2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-5 and 7-11 and species: breast cancer cell and blocking peptide, in the reply filed on 03/29/2007 is acknowledged. The traversal is on the ground(s) that Groups I and II be examined together because the methods for disrupting survival signaling from the microenvironment to cancer cells, are fundamentally related to the methods of inhibiting cellular proliferation or inducing cell death or cellular differentiation. This is found persuasive, therefore Group II, claims 12, 13, 47, 49-54, will be examined with Group I.

2. Claims 55-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 03/29/2007.

3. Claims 7, 8, 10, and 11, 47, 50, 51, and 52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 03/29/2007.

4. Claims 2, 6, 14-46, and 48 have been canceled by applicant

5. Claims 1, 3, 4, 5, 9, 12,13, 49, 53, and 54 will be examined on the merits.

Claim Objections

6. Claim 54 is objected to because of the following informalities: Claim 54 depends from withdrawn Claim 50, which has been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, 3, 4, 5, and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1 is vague and indefinite because the method recites signaling from the microenvironment to "cancer cells", but also refers to hyperproliferative disorders ~~not involving cancer such as~~ THAT ENCOMPASS rheumatoid arthritis and psoriasis (specifications p. 18). It is also unclear whether the "microenvironment" is that of the cancer cells or any cell in which survival signaling is disrupted.

b) Claim 1 is vague and indefinite because it is unclear whether the result of "sensitizing the cells" is referring to sensitizing said cells to chemotherapy, biological therapies, radiation therapy, *and* hyperproliferative disorders? These are all included in the wherein clause and it is unclear what are the metes and bounds of the claim.

b) Claims 1 recites "hyperproliferative disorders in a mammal", however the active steps of the method read on an *in vitro* assay. The metes and bounds of the

claim are unclear in the absence of limitations specifying whether "in a mammal" refers to just hyperproliferative disorders or to the active steps of the claim itself.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 5, 9, 12, 13, 49, 53 and 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for disrupting survival signaling by administering an agent that downregulates alpha 5 beta 1 *in vitro* and a method for blocking the interaction of alpha 5 beta 1 with the extracellular matrix protein, fibronectin, with a peptide in breast cancer cells *in vitro*, does not reasonably provide enablement for downregulating just any integrin or blocking the interaction of just any integrin with just any extracellular matrix protein and disrupting hyperproliferative disorders other than breast cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or

unpredictability of the art, and (8) the breadth of the claims. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

The applicant broadly claims a method for disrupting survival signaling by administering ***any*** agent that downregulates ***any*** integrin and a method for disrupting survival signaling by administering ***any*** agent that is effective in blocking the interaction of ***any*** integrin with ***any*** extracellular matrix protein associated with ***any*** cancer or hyperproliferative disorder.

a) The number of working examples and guidance provided by applicant is insufficient to enable the broad scope of the claims. Applicant has only provided working examples for the downregulation of alpha 5 beta 1 and the interaction between the integrin alpha 5 beta 1 and the extracellular matrix protein fibronectin in breast cancer cells. This single example is not indicative of an ability to predictably practice the invention as claimed with regard to all integrins and all extracellular matrix proteins. "Given that cell proliferation (survival signaling) is regulated by intricate cross-talk of multiple signals from the cell surface receptors for growth factors/cytokines and those from adhesion receptors like integrins, it is possible that different cell types respond differently to the signals transduced by ligand-occupied alpha 5 beta 1. In tumor cells, several lines of evidence indicate that the integrin alpha 5 beta 1 **negatively** regulates cell proliferation" (Akamatsu et al. Cancer Research 1996). Akamatsu et al. teaches that interaction of integrin alpha 5 beta 1 with fibronectin transduces signals that suppress anchorage-independent tumor cell (HT1080 fibrosarcoma) growth in soft agar

and tumor growth *in vivo* (p. 4545, right column). In line with these observations, Schreiner et al. (Cancer Research 1991) teaches there is an inverse correlation between the level of expression of the alpha 5 beta 1 fibronectin receptor and the rate of tumor growth *in vivo*. Variants of Chinese hamster ovary cells deficient in or with reduced levels of integrin alpha 5 beta 1 showed increased tumorigenicity and tumors from clones expressing very low levels of fibronectin receptor grew most rapidly. These findings are **not** in accordance with the teachings of the Applicant and support the unpredictability of the broad scope of the claim to include any cancer or hyperproliferative disorder.

Applicant also claims that by performing the active method steps of administering an agent effective in blocking the interaction of an integrin with an extracellular matrix protein you are inherently "sensitizing cells to chemotherapy, biological therapies or radiation therapy of primary tumors, cancer metastases or micrometastases". However, applicant merely states that disrupting survival signaling from the microenvironment in cancer cells results in sensitizing cells (specifications p. 23 section [0082]) but does not provide any evidence or working examples to support this claim. Undue experimentation would be required to support this limitation.

b) The "predictability or unpredictability of the art" does not support a finding of enablement. All evidence stated in the application is *in vitro* data. The application nowhere provides any working examples of *in vivo* results supporting the claimed invention that administering to a subject an agent which blocks the interaction of an integrin with an extracellular matrix protein will disrupt survival signaling. It is also well

known in the art that cancer treatment is an unpredictable art in itself. Zips et al. [In Vivo. 2005 Jan-Feb;19(1):1-7.] discloses; "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularization, perfusion and, thereby drug access to the tumor cells are not evenly distributed and this fact 'consists' of an important source of heterogeneity in tumor response to drugs that does not exist *in vitro*. Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluation in animal tumor systems is essential."

Therefore, the skilled artisan seeking to administer a blocking peptide to disrupt survival signaling by blocking the interaction of an integrin with an extracellular matrix protein as a treatment method for a subject with cancer would have to engage in undue experimentation to determine how to practice/use the claimed invention.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 4, 5, 9, 12, 13, 49, 53, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Bates et al. (Cancer and Met. Review 1995, cited on 892 02/28/2007). Claims 1, 3, 4, 5, 9, 12, 13, 49, 53, and 54 recite a method for inhibiting cellular proliferation and disrupting survival signaling from the microenvironment to

breast cancer cells by administering a blocking peptide that effectively blocks the interaction of integrin alpha 5 beta 1 with the extracellular matrix protein, fibronectin. Bates et al. teaches the involvement of integrins in cell survival and that apoptosis can be induced experimentally by blocking integrin binding to specific components of the extracellular matrix (p. 193-194, Section: "Integrins and protection from apoptosis"). The reference teaches the active steps claimed therefore by performing the active steps of blocking the interaction of the integrin with the extracellular matrix protein one would inherently be "sensitizing cells to chemotherapy, biological therapies or radiation therapy" as evidence by the specification (p.18). The reference meets each and every limitation of the claims.

10. Claims 1, 3, 4, 5, 9, 12, 13, 49, 53, and 54 are rejected under 35. U.S.C. 102(b) as being anticipated by Nista et al. (Int. J. Cancer 1997). Claims 1, 3, 4, 5, 9, 12, 13, 49, 53, and 54 recite a method for inhibiting cellular proliferation and disrupting survival signaling from the microenvironment to breast cancer cells by administering a blocking peptide that effectively blocks the interaction of integrin alpha 5 beta 1 with the extracellular matrix protein, fibronectin.

Nista et al. teaches the functional role of alpha 5 beta 1 integrin fibronectin receptor expressed on adriamycin-resistant MCF-7 human mammary carcinoma cells. Cell cycle analysis demonstrated that cell/FN interaction induces the re-entry of ADR^R MCF-7 into S phase, and prevents them from undergoing serum deprivation-induced apoptosis. Treatment with GRGDSP-containing synthetic peptide, which blocks the interaction of alpha 5 beta 1 with fibronectin, was used to confirm these results (p. 139,

right column, 1st paragraph). The role of alpha 5 beta 1 in mediating FN-derived mitogenic signals was shown by the inhibition of the proliferative response following cell treatment with GRGDSP-containing synthetic peptide. The reference teaches the active steps claimed therefore by performing the active steps of blocking the interaction of the integrin with the extracellular matrix protein one would inherently be "sensitizing cells to chemotherapy, biological therapies or radiation therapy" as evidence by the specification (p.18). The reference meets each and every limitation of the claims.

Conclusion

11. No Claim is allowed.

12. Claim 53 is also objected to for depending from non-elected claim 50. see ip 6

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Meera Natarajan Ph.D. whose telephone number is 571-270-3058. The examiner can normally be reached on Monday-Thursday, 8:30AM-6:00PM, ALT. Friday. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mary Mosher can be reached on 571-272-0906. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For

more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MN

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SUPERVISORY PATENT EXAMINER